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(54) Title: CONTROLLED RELEASE, MULTIPLE UNIT DRUG DELIVERY SYSTEMS

(57) Abstract: The invention relates to controlled release multiple unit system of carvedilol for oral administration, and methods of preparing the system, which can be easily compressed into tablets or filled into capsules or sachets without affecting the desired release characteristics of the pharmaceutical active ingredient incorporated within the system. The multiple unit system includes multiple units. Each unit includes at least one core and having an outer surface; a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including carvedilol; a second rate controlling coating layer surrounding at least a portion of the outer surface of the first coating layer and having an outer surface, the coating layer including one or more sustained release polymers and one or more enteric polymers. The multiple unit system may optionally contain a seal coat between inert core and carvedilol layer, or between carvedilol layer and rate controlling polymer layer. The units are finally compressed into tablet or filled into capsule/sachet.

CONTROLLED RELEASE, MULTIPLE UNIT DRUG DELIVERY SYSTEMS

Field of the Invention

The technical field of the invention relates to controlled release multiple unit system of carvedilol for oral administration, and methods of preparing the system, which can be easily compressed into tablets or filled into capsules or sachets without affecting the desired release characteristics of the pharmaceutical active ingredient incorporated within the system.

Background of the Invention

Carvedilol is a non-selective β-adrenergic blocking agent with α_1-blocking activity. It is indicated alone or in combination with digitalis, diuretics or ACE inhibitors for the treatment of congestive heart failure and hypertension.

Chemically, Carvedilol is 1 - (9H – Carbazol – 4 - yloxy) – 3 – [[2 – (2 – methoxy phenoxy) ethyl] amino] – 2 – propanol and is used as a racemic mixture. Carvedilol is insoluble in water. Further, its solubility is pH dependent, with a comparatively higher solubility at gastric pH and lower at intestinal pH.

Presently, carvedilol is marketed by GlaxoSmithkline under the trade name Coreg® in 3.125 mg, 6.25mg and 12.5mg strengths. Coreg® is a conventional immediate release tablet intended for twice daily administration. When administered, the tablet disintegrates and releases all of its contents into the stomach so that when carvedilol leaves the stomach, it is either in solution or in the form of a suspension, i.e. in a readily absorbable form.

However, in most of the cases it is difficult for the patients to stick to the stringent twice-daily administration routine, leading to instances of missed doses very often. As a consequence, the pharmacokinetic profile of carvedilol may fall below the minimum therapeutic level, causing improper treatment and/or development of tolerance. Such patient incompliance can be minimized by the use of controlled release formulations of carvedilol.

Controlled release formulations of carvedilol having more or less uniform rate of release throughout the gastrointestinal tract are disclosed in the prior art, using various polymers in matrices or in release controlling coating layers, for example, PCT application No. WO 99/24017 discloses matrix formulation of carvedilol, wherein the matrix core is

comprised of a multitude of pellets coated independently with different release delaying substances, which can be directly compressed into tablet or placed in capsules. U.S. Patent No. 6,475,493 discloses a coating composition for a controlled release pharmaceutical composition. The coating composition comprises a mixture of at least 75 % by weight of a water insoluble polymer, which is insoluble at both acidic as well as basic pH and 1 to 25 % by weight of an enteric polymer which is substantially insoluble in water at a pH below 4.5, said coating composition being a heterogeneous mixture.

The normal pH in human gastrointestinal tract varies from about 1 (in fasted stomach) to about 8 (in lower large intestine). For drugs like carvedilol, having decreasing solubility with increasing pH it is necessary to formulate controlled release drug delivery devices with higher release rates in the intestine. This is important to cope with the decreasing solubility of the drug in the intestine.

Therefore, controlled release formulations of carvedilol, which can provide higher release rates at intestinal pH, are particularly needed.

Summary of the Invention

In one general aspect there is provided a multiple dosage form that includes multiple units. Each unit includes at least one core and having an outer surface; a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including carvedilol; a second rate controlling coating layer surrounding at least a portion of the outer surface of the first coating layer and having an outer surface, the coating layer including one or more sustained release polymers and one or more enteric polymers.

The core may include one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose. The sugar may include one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose. The core may include one or more of an insoluble material, a soluble material, and a swellable material.

The rate controlling layer may include one or more of sustained release polymers and one or more enteric polymers. The sustained release polymer may include one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose;

waxes; methacrylic acid copolymers such as Eudragit ® RL, NE and RS; and mixtures thereof.

The enteric polymer may include one or more of cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L30 D-55, Eudragit® L 100, and Eudragit® S 100, and mixtures thereof.

The multiple unit dosage form may further include one or more additional layers. The additional layers are positioned (a) between the core and the first coating layer and surrounding at least a portion of the core, (b) between the first coating layer and the second rate controlling coating layer and surrounding at least a portion of the first coating layer, and (c) over the second rate controlling coating layer and surrounding at least a portion of the second coating layer. The one or more additional layers include one or more of a seal coat. The seal coat may be one or more of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, and methacrylic acid copolymers.

In the multiple unit dosage form, one or more of the core, the first coating layer, and the second coating layers may include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers, and coloring agents. The surfactants may include one or more of a non-ionic surfactant, an ionic surfactant, mono fatty acid esters of polyoxyethylene sorbitan, polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20), an anionic surfactant, sodium lauryl sulfate, polyoxyethylene castor oil derivative, polyoxyethyleneglycerol triiricinoleate castor oil, polyoxyl 35 castor oil, Cremophor EL, and Vitamin E TPGS, d-alpha-tocopheryl polyethylene glycol 1000 succinate, polyethoxylated fatty acids and their derivatives, polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4–150 mono dilaurate, polyethylene glycol –20 glyceryl stearate, alcohol – oil transesterification products, polyethylene glycol – 6 corn oil, polyglycerized fatty acids, polyglyceryl – 6 pentaoleate, propylene glycol fatty acid esters, propylene glycol monocaprylate, mono and diglycerides, glyceryl ricinoleate, sterol and sterol derivatives, sorbitan fatty acid esters and their derivatives, polyethylene glycol – 20

sorbitan monooleate and sorbitan monolaurate, polyethylene glycol alkyl ether or phenols, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol, sugar esters, sucrose monopalmitate, polyoxyethylene – polyoxypropylene block copolymers, poloxamer, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine.

The binders may include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, and propylene glycol. The diluents may include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, and sugar confectioners. The disintegrants include one or more of starch, croscarmellose, crospovidone, and sodium starch glycolate. The lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, and white beeswax. The plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, and dibutyl sebacate. The stabilizers include one or more of antioxidants, buffers, and acids.

The multiple unit dosage form may further include one or more pharmaceutically acceptable excipients around the individual units. The dosage form may be a tablet and the tablet may be formed by application of a compressive force. The dosage form may be a capsule.

In another general aspect there is provided a controlled release dosage form that includes multiple units. Each unit includes at least one core coated with a carvedilol layer; and a rate controlling polymer layer including one or more sustained release polymers and one or more enteric polymers.

In another general aspect there is provided a controlled release dosage form that includes multiple units. Each unit includes at least one core coated with a carvedilol layer; and a rate controlling polymer layer including one or more sustained release polymers and

one or more enteric polymers, wherein the rate controlling polymer layer is applied as a homogeneous coating composition.

In another general aspect there is provided a multiple dosage form that includes multiple units. Each unit includes at least one core and having an outer surface; a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including carvedilol; a second controlled release coating layer surrounding at least a portion of the outer surface of the first coating layer and having an outer surface, the coating layer including one or more sustained release polymers and one or more enteric polymers, wherein the second coating layer is applied as a homogeneous coating composition.

In another general aspect, there is provided a process for the preparation of a multiple unit dosage form. The process includes providing at least one core having an outer surface, forming a coated core by applying one or more coating layers to the core such that the one or more coating layers surround at least a portion of the outer surface of the core or the coating layers, forming an individual unit, and combining one or more units to form a multiple unit dosage form. The coating layers include one or more sustained release polymers and one or more enteric polymers, and active pharmaceutical ingredients.

Embodiments of the process may include one or more of the following features. For example, the process may further include applying one or both of a seal layer between the core and the coating layer, between the one or more coating layers, and over the coating layers.

The core may be an inert core. The core may include pharmaceutically acceptable inert cores available commercially or from inert material by process of extrusion-spheronization, granulation and the like. The inert core may be of any geometric shape, in particular spheres for ease of uniform coating. The inert core diameter may vary from about 100 to 2000μm.

The core may be prepared by extrusion-spheronization. The extrusion-spheronization process may include granulating an inert core material with or without other pharmaceutical excipients with a binder solution to form a wet mass, passing the wet mass through an extruder to form extrudates, and spheronizing the extrudates. The core may be prepared by granulation. The granulation process may include wetting a dry mix of core material with or without other pharmaceutical excipients with a binder solution.

The units may be prepared by coating the cores with carvedilol and sustained release polymers and enteric polymers. The units may be prepared by coating cores with a first layer comprising an active pharmaceutical ingredient and a second outer layer comprising a sustained release polymer and enteric polymers.

The process may further include applying a seal coat between the core and the subsequent layers. The process may further include applying a seal coat between a layer comprising an active pharmaceutical ingredient and a layer comprising a sustained release and enteric polymers.

The rate controlling layer may include one or more of sustained release polymers and one or more enteric polymers. The sustained release polymer may include one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, Eudragit ® RL, NE and RS, and mixtures thereof.

The enteric polymer may include one or more of cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L30 D-55, Eudragit® L 100, and Eudragit® S 100, and mixtures thereof.

In another general aspect, there is provided a method for treating congestive heart failure and/or hypertension in a subject, by administering to said subject a controlled release multiple unit system of carvedilol comprising an inert core coated with a carvedilol layer; and a rate controlling polymer layer including one or more sustained release polymers and one or more enteric polymers.

In another general aspect, there is provided a method for treating congestive heart failure and/or hypertension in a subject, by administering to the said subject a controlled release multiple unit system of carvedilol comprising an inert core coated with a carvedilol layer; and a rate controlling polymer layer including one or more sustained release polymers and one or more enteric polymer, wherein the rate controlling polymer layer is applied as a homogeneous coating composition.

Embodiments of the controlled release multiple unit system may include one or more of the following features. For example, the system may be a tablet or a capsule. The

units can be compressed into tablet, or filled into a capsule or a sachet; without affecting the desired release characteristics of drug.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have found that the use of a combination of sustained release polymer and enteric polymer in the rate controlling polymer layer helps to achieve the desired release profile for insoluble basic drugs having comparatively lower solubility at higher pH. The inventors have also found that coating a solid medicament in a pharmaceutical composition with a homogenous coating composition of rate controlling polymers comprising one or more sustained release polymers and one or more enteric polymers provide a better control over the rate of release of drug. The homogeneous coating composition is easy to apply and also provides a uniform coating with a smooth appearance.

The inventors have developed separate multiple unit dosage form or systems of carvedilol that are in the form of controlled release tablets. The term "controlled release" as used herein includes any type of modified release such as prolonged release, delayed release, sustained release, extended release, and the like.

In general, the multiple units can be for use in any dosage forms, such as a tablet, capsule or sachet, and include a core or pellet, and one or more layers around the core or pellet. The core or pellet can be an inert material. The layers around the core may include one or more release or rate controlling polymers and/or active pharmaceutical ingredients. The layers also may be in the form of sealing around or between the polymer and active pharmaceutical ingredients. The various layers may optionally contain pharmaceutically acceptable excipients.

The multiple units of the multiple unit systems may contain inert pellets or cores. Cores and pellets generally are used interchangeably herein. The inert core of the multiple unit systems is either a commercially available product or prepared in the laboratory. The inert core may be of any geometric shape, although spherical beads have the advantage of providing ease of uniform coating. The bead diameter may vary from about 100 μm to 2000 μm.

The core may be prepared by extrusion-spheronization. The extrusion-spheronization process may include granulating an inert core material with or without other pharmaceutical excipients with a binder solution to form a wet mass, passing the wet mass through an extruder to form extrudates, and spheronizing the extrudates. The core may be prepared by granulation. The granulation process may include wetting a dry mix of core material with or without other pharmaceutical excipients with a binder solution.

The material from which the inert pellet or core is prepared may be selected from one or more of pharmaceutically inert insoluble, soluble, and/or swellable materials, with or without pharmaceutically acceptable excipients. The insoluble inert core material may be, for example, one or more of sand (silicon dioxide), glass, microcrystalline cellulose (e.g., celpheres) or plastic (e.g., polystyrene) material. The soluble inert core material may be, for example, one or more sugar such as glucose, mannitol, lactose, xylitol, dextrose, sucrose, and the like. The swellable inert core material may be, for example, hydroxypropyl methylcellulose or a similar material. The core also can be a combination of two or more of these three general types of core materials.

The controlled release multiple units may be prepared from inert cores by (a) coating the inert core with carvedilol and rate controlling polymer layers; or (b) coating the inert core with one or more carvedilol layers and rate controlling polymer layers separately. Both of these options may contain a seal coat between the inert core and the carvedilol layer and/or between the carvedilol layer and the rate controlling polymer layer.

The controlled release units prepared by any of the above methods can be mixed with other pharmaceutically acceptable excipients, to the extent required or desired, and compressed into tablets or filled into capsules and sachets using techniques known in the art for these purposes. The final tablets or capsules may optionally be coated, if desired.

The carvedilol layer may be applied as an aqueous or non-aqueous solution or dispersion of drug in water or organic solvent, or mixtures thereof.

The rate controlling polymer layer includes one or more of sustained release polymers and one or more of enteric polymers with or without other pharmaceutically acceptable excipients. This layer may be applied as an aqueous or non-aqueous solution or dispersion of polymers in a water or organic solvent. Suitable sustained release polymers include one or more of cellulosic polymers such as ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose,

carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose; methacrylic acid polymers such as Eudragit ® RL and RS; and mixtures thereof.

The enteric polymer may include one or more of cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L30 D-55, Eudragit® L 100, and Eudragit® S 100; and mixtures thereof.

The seal coat may include suitable polymers, such as hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methacrylic acid copolymers, and the like. Seal layer generally are applied to separate two incompatible layers, provide protection from moisture, etc. In general, the seal layers may be the same or similar polymers used in different combinations or concentrations.

The other pharmaceutically acceptable excipients as used herein include surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers and coloring agents.

Suitable surfactants include one or more of non-ionic and ionic (i.e., cationic, anionic and Zwitterionic) surfactants suitable for use in pharmaceutical compositions. For example, suitable surfactants include non-ionic surfactants such as mono fatty acid esters of polyoxyethylene sorbitan (e.g., polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20)); anionic surfactants (e.g., sodium lauryl sulfate); polyoxyethylene castor oil derivatives (e.g., polyoxyethyleneglycerol triiricinoleate or polyoxyl 35 castor oil (Cremophor EL)); and Vitamin E TPGS (d-alpha-tocopheryl polyethylene glycol 1000 succinate). Other suitable surfactants include polyethoxylated fatty acids and their derivatives (e.g., polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4–150 mono dilaurate, and polyethylene glycol – 20 glyceryl stearate); alcohol – oil transesterification products (e.g., polyethylene glycol – 6 corn oil); polyglycerized fatty acids (e.g., polyglyceryl – 6 pentaoleate); propylene glycol fatty acid esters (e.g., propylene glycol monocaprylate); mono and diglycerides (e.g., glyceryl ricinoleate); sterol and sterol derivatives; sorbitan fatty acid esters and their derivatives (e.g., polyethylene glycol – 20 sorbitan monooleate and sorbitan monolaurate);

polyethylene glycol alkyl ether or phenols (e.g., polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol); sugar esters (e.g., sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"); and ionic surfactants (e.g., sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine).

Suitable binders include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Suitable diluents include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and mixtures thereof.

Suitable disintegrants include one or more of starch, croscarmellose, crospovidone, sodium starch glycolate and the like. Suitable lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax and the like. Suitable plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, dibutyl sebacate and the like. Suitable stabilizers include one or more of antioxidants, buffers, acids and the like. Suitable coloring agents include any FDA approved colors for oral use.

The multiple unit, controlled release tablet of carvedilol can be prepared by processes known in the relevant art, e.g., comminuting, mixing, granulating, sizing, filling, molding, spraying, immersing, coating, compressing, etc.

In one of the embodiments, the multiple units, controlled release tablets of carvedilol can be prepared by coating inert pellets or cores with one or more carvedilol layers which are further coated with a controlled release polymer layer. Optionally, the controlled release layer may also be coated with a seal coat to form the individual units. Further, these coated pellets or cores, or the units, may be blended with pharmaceutically acceptable excipients and compressed into suitably sized, multiple unit tablets.

When administered the individual units are dispersed freely into the gastrointestinal contents. In the acidic environment of the gastric fluids, release of carvedilol is controlled by the sustained release polymer(s). As the enteric polymer(s) do not dissolve in the stomach, the release of carvedilol is at a slower rate. Gradually, as the pH of release environment increases with the movement of the multiple units into the intestine, the enteric polymer starts dissolving. This dissolution of the enteric polymer increases the release rate of carvedilol markedly. The increase in release rate nullifies the decrease in absorption rate due to decrease in solubility of carvedilol and thereby a uniform plasma concentration is maintained over a long period of time.

The multiple unit system of the present invention has added advantages of division of doses without formulation and process changes, and a performance which is independent of variations in gastric emptying rate.

Carvedilol layer may comprise therapeutically effective amount of free carvedilol base or any pharmaceutically acceptable salt thereof, with or without other pharmaceutically inert excipients. In particular, carvedilol free base may be used.

The rate controlling polymer layer may comprise of sustained release polymer(s) and enteric polymer(s) with or without other pharmaceutically inert excipients. The amount of the rate controlling polymers may vary from about 1 % to about 100 % by weight of the total weight of carvedilol coated core. The w/w ratio of sustained release polymer and enteric release polymer may vary in the range of about 1:10 to about 10:1, in particular about 10:1 to about 1:1.

In one of the embodiments, controlled release multiple unit system of carvedilol can be prepared by a process comprising the steps of:

a) coating inert core with carvedilol and rate controlling polymer layer; and

b) filling into suitable sized capsules.

In one of the embodiments, controlled release multiple unit system of carvedilol can be prepared by a process comprising the steps of:

a) coating inert core with carvedilol and rate controlling polymer layer;

b) coating with carvedilol layer for immediate release; and

c) filling into suitable sized capsules.

In another embodiment, controlled release multiple unit system of carvedilol can be prepared by a process comprising the steps of:

a) coating inert core with carvedilol and rate controlling polymer layer;

b) applying a seal coat layer between inert core and carvedilol layer; and

c) processing into a solid dosage form.

In another embodiment, controlled release multiple unit system of carvedilol can be prepared by a process comprising the steps of:

a) coating inert core with carvedilol and rate controlling polymer layer;

b) applying a seal coat layer between carvedilol layer and rate controlling polymer layer; and

c) processing into a solid dosage form.

In another embodiment, controlled release multiple unit system of carvedilol can be prepared by a process comprising the steps of:

a) coating inert core with carvedilol and rate controlling polymer layer;

b) applying seal coat layers between inert core and carvedilol layer, and carvedilol layer and rate controlling polymer layer; and

c) processing into a solid dosage form.

The carvedilol and seal coat layers can be applied over the inert cores as solution/ suspension of coating ingredients using any conventional technique known in the prior art such as spray coating in a conventional coating pan or fluidized bed processor; dip coating and the like. The rate controlling polymer layer may be applied as a solution of rate controlling polymers, with or without other pharmaceutically inert excipients dissolved or dispersed in the solution.

Alternatively, the layers over the inert core can also be applied using hot melt technique.

Example of solvents used for preparing a solution of rate controlling polymers and solution/suspension of coating ingredients of other layers include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water, and mixtures thereof.

The controlled release units prepared by any of the above methods can be blended with other pharmaceutically inert excipients, if required and compressed into tablet or filled into capsule/sachet, using techniques known in the art for these purposes. The final tablet or capsule may optionally be coated with film-forming polymers and/or carvedilol for immediate release, if desired.

The multiple unit systems described above are further illustrated by the following examples. Although these examples are illustrative of the techniques, compositions, and concepts described herein, they are not intended to be limiting.

Example 1

(i) Inert core	
Non pareil seed	300 mg
(ii) Drug layer	
Carvedilol	50 mg
Lactose	50 mg
Tween 80	3 mg
Polyvinyl pyrrolidone	4 mg
Aerosil	3 mg
iii) Rate controlling layer	
Ethyl cellulose	24 mg
Hydroxypropyl methylcellulose	4.8 mg
Eudragit® L-100-55	6.0 mg
Triacetin	1.8 mg
Talc	1.2 mg

Procedure:

1. A dispersion of drug in water was prepared by adding carvedilol, polyvinyl pyrrolidone, tween and lactose in water with continuous stirring using a mechanical stirrer.
2. Non-pareil seeds were loaded in Glatt and coated with drug dispersion of step 1.
3. A solution of ethyl cellulose, hydroxypropyl methylcellulose, Eudragit® L 100-55 and triacetin was prepared in a mixture of isopropyl alcohol, methylene chloride and water (60:30:10) into which talc was dispersed.

4. Drug loaded seeds of step 2 were then coated with dispersion of step 3 using a Glatt to obtain the controlled release units.

5. Controlled release multiple units of step 4 were then filled into capsules of appropriate size.

Table 1 illustrates the release pattern in vitro for capsules prepared according to Example 1; using USP apparatus – II, at 50 rpm, and changeover media in which pH was changed from 1.2 (for 1 hour) to 4.5 (for 1 hour) and 6.8 (for 6 hours).

Table 1. *In vitro* release pattern of capsules; using USP apparatus – II, at 50 rpm, and changeover media in which pH was changed from 1.2 (for 1 hour) to 4.5 (for 1 hour) and 6.8 (for 6 hours).

Time (Hours)	Cumulative percentage release of carvedilol from capsules
1	12
2	30
4	42
4	60
6	80
8	98

Example 2

(i) Inert core

Non pareil seed	300 mg

(ii) Drug layer

Carvedilol	50 mg
Lactose	50 mg
Tween 80	3 mg
Polyvinyl pyrrolidone	4 mg
Aerosil	3 mg

iii) Rate controlling layer

Ethyl cellulose	12 mg
Hydroxypropyl methylcellulose	3 mg
Eudragit® L-100-55	3.6 mg
Triacetin	0.9 mg

Procedure:

1. A dispersion of drug in water was prepared by adding carvedilol, polyvinyl pyrrolidone, tween and lactose in water with continuous stirring using a mechanical stirrer.
2. Non-pareil seeds were loaded in Glatt and coated with drug dispersion of step 1.
3. A solution of ethyl cellulose, hydroxypropyl methylcellulose, Eudragit® L 100-55 and triacetin was prepared in a mixture of isopropyl alcohol, methylene chloride and water (60:30:10).
4. Drug loaded seeds of step 2 were then coated with solution of step 3 using a Glatt to obtain the controlled release units.
5. Controlled release multiple units of step 4 were then filled into capsules of appropriate size.

Table 2 illustrates the release pattern in vitro for capsules prepared according to Example 2; using USP apparatus – II, at 50 rpm, and changeover media in which pH was changed from 1.2 (for 1 hour) to 4.5 (for 1 hour) and 6.8 (for 6 hours).

Table 2. *In vitro* release pattern of capsules; using USP apparatus – II, at 50 rpm, and changeover media in which pH was changed from 1.2 (for 1 hour) to 4.5 (for 1 hour) and 6.8 (for 6 hours).

Time (Hours)	Cumulative percentage release of carvedilol from capsules
1	10
2	36
3	53
4	72
6	87
8	89

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. For example, all the working examples involve the use of carvedilol as the drug in controlled release multiple unit systems but we believe the system to work even with other drugs that

are insoluble and in addition exhibit a pH dependent solubility, particularly with drugs having a decreased solubility with increasing pH. Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

We Claim:

1. A multiple unit dosage form comprising multiple units, each unit comprising: at least one core having an outer surface;

a first coating layer surrounding at least a portion of the outer surface of the core and having an outer surface, the coating layer including carvedilol; and

a second rate controlling coating layer surrounding at least a portion of the outer surface of the first coating layer and having an outer surface, the coating layer including one or more sustained release polymers and one or more enteric polymers.

2. The multiple unit dosage form of claim 1, wherein the core includes one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose.

3. The multiple unit dosage form of claim 2, wherein the sugar comprises one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose.

4. The multiple unit dosage form of claim 1, wherein the core comprises one or more of an insoluble material, a soluble material, and a swellable material.

5. The multiple unit dosage form of claim 1, wherein the sustained release polymer comprises one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and mixtures thereof.

6. The multiple unit dosage form of claim 5, wherein the sustained release polymer is a combination of ethyl cellulose and hydroxypropyl methylcellulose.

7. The multiple unit dosage form of claim 1, wherein the enteric polymer comprises one or more of cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers, and mixtures thereof.

8. The multiple unit dosage form of claim 7, wherein the enteric polymer is a methacrylic acid copolymer.

9. The multiple unit dosage form of claim 1, further comprising one or more additional layers, wherein the additional layers are positioned (a) between the core and the first coating layer and surrounding at least a portion of the core, (b) between the first coating layer and the second rate controlling coating layer and surrounding at least a portion of the first coating layer, and (c) over the second rate controlling coating layer and surrounding at least a portion of the second coating layer,

wherein the one or more additional layers comprise one or more of a seal coat.

10. The multiple unit dosage form of claim 9, wherein the seal coat comprises one or more of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, and methacrylic acid copolymers.

11. The multiple unit dosage form of claim 1, wherein one or more of the core, the first coating layer, and the second rate controlling coating layer includes one or more pharmaceutically acceptable excipients.

12. The multiple unit dosage form of claim 11, wherein the pharmaceutically acceptable excipients includes surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers, and coloring agents.

13. The multiple unit dosage form of claim 12, wherein the surfactants include one or more of a non-ionic surfactant, an ionic surfactant, mono fatty acid esters of polyoxyethylene sorbitan, polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (20) sorbitan monolaurate (Tween 20), an anionic surfactant, sodium lauryl sulfate, polyoxyethylene castor oil derivative, polyoxyethyleneglycerol triiricinoleate castor oil, polyoxyl 35 castor oil, Cremophor EL, and Vitamin E TPGS, d-alpha-tocopheryl polyethylene glycol 1000 succinate, polyethoxylated fatty acids and their derivatives, polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4–150 mono dilaurate, polyethylene glycol –20 glyceryl stearate, alcohol – oil transesterification products, polyethylene glycol – 6 corn oil, polyglycerized fatty acids, polyglyceryl – 6 pentaoleate, propylene glycol fatty acid esters, propylene glycol monocaprylate, mono and diglycerides, glyceryl ricinoleate, sterol and sterol derivatives, sorbitan fatty acid esters and their derivatives, polyethylene glycol – 20 sorbitan monooleate and sorbitan

monolaurate, polyethylene glycol alkyl ether or phenols, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol, sugar esters, sucrose monopalmitate, polyoxyethylene – polyoxypropylene block copolymers, poloxamer, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine.

14. The multiple unit dosage form of claim 12, wherein the binders includes one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, and propylene glycol.

15. The multiple unit dosage form of claim 12, wherein the diluents include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, and sugar confectioners.

16. The multiple unit dosage form of claim 12, wherein the disintegrants include one or more of starch, croscarmellose, crospovidone, and sodium starch glycolate.

17. The multiple unit dosage form of claim 12, wherein the lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, and white beeswax.

18. The multiple unit dosage form of claim 12, wherein the plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, and dibutyl sebacate and the stabilizers include one or more of antioxidants, buffers, and acids.

19. The multiple unit dosage form of claim 1, wherein the dosage form comprises a tablet.

20. The multiple unit dosage form of claim 19, wherein the tablet further includes one or more pharmaceutically acceptable excipients around the individual units.

21. The multiple unit dosage form of claim 1, wherein the dosage form comprises a capsule.

22. A controlled release multiple unit system of carvedilol comprising an inert core coated with a carvedilol layer; and a rate controlling polymer layer comprising at least one sustained release polymer and one enteric polymer.

23. The controlled release multiple unit system of claim 22, wherein the rate controlling polymer layer is applied as a homogeneous coating composition.

24. The controlled release multiple unit system of claim 22 or 23, wherein one or more seal coat layers are positioned between inert core and carvedilol layer, and/or carvedilol layer and rate controlling polymer layer and/or over the rate controlling polymer layer.

25. The controlled release multiple unit system of claim 22, wherein the carvedilol comprises one or more of free carvedilol base or a pharmaceutically acceptable salt thereof.

26. The controlled release multiple unit system of claim 25, wherein the carvedilol is a free carvedilol base.

27. The controlled release multiple unit system of claim 22, wherein the inert core comprises one or more of sugar sphere, a non pareil seed, and celphere.

28. The controlled release multiple unit system of claim 27, wherein the inert core is a non pareil seed.

29. The controlled release multiple unit system of claim 22, wherein the inert core comprises one or more of an insoluble, a soluble, or a swellable inert material.

30. The controlled release multiple unit system of claim 29, wherein the inert core is an insoluble material.

31. The controlled release multiple unit system of claim 30, wherein the insoluble material comprises one or more of sand (silicon dioxide), glass, microcrystalline cellulose, and plastic (polystyrene).

32. The controlled release multiple unit system of claim 29, wherein the inert core is a soluble material.

33. The controlled release multiple unit system of claim 32, wherein the soluble material comprises one or more of sugars such as glucose, mannitol, lactose, xylitol, sucrose, and dextrose.

34. The controlled release multiple unit system of claim 29, wherein the inert core is a swellable material.

35. The controlled release multiple unit system of claim 34, wherein the swellable material is hydroxypropyl methylcellulose.

36. The controlled release multiple unit system of claim 29, wherein the inert core is prepared by a method of extrusion-spheronization.

37. The controlled release multiple unit system of claim 29, wherein the inert core is prepared by a method of granulation.

38. The controlled release multiple unit system of claim 22, wherein the sustained release polymer comprises one or more of cellulosic polymers such as ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose; waxes; methacrylic acid copolymers; and mixtures thereof.

39. The controlled release multiple unit system of claim 38, wherein the sustained release polymer is a combination of ethyl cellulose and hydroxypropyl methylcellulose.

40. The controlled release multiple unit system of claim 22, wherein the enteric polymer comprises one or more of cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers; and mixtures thereof.

41. The controlled release multiple unit system of claim 40, wherein the enteric polymer is a methacrylic acid copolymer.

42. The controlled release multiple unit system of claim 24, wherein the seal coat comprises one or more of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methacrylic acid copolymers, and mixtures thereof.

43. The controlled release multiple unit system of claim 22, wherein one or more of the core, the first coating layer, and the second rate controlling coating layer includes one or more pharmaceutically acceptable excipients.

44. The controlled release multiple unit system of claim 43, wherein pharmaceutically acceptable excipients includes surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers, and coloring agents.

45. The controlled release multiple unit system of claim 22, wherein the multiple unit system is a solid dosage form comprisisng a tablet, a capsule, or a sachet.

46. The controlled release multiple unit system of claim 45, wherein the solid dosage form is a capsule.

47. A process for the preparation of a multiple unit dosage form, the process comprising:

providing at least one core having an outer surface;

forming a coated core by applying one or more coating layers to the core such that the one or more coating layers surround at least a portion of the outer surface of the core or the coating layers;

forming an individual unit;

combining one or more units to form a multiple unit dosage form,

wherein the coating layers include one or more rate controlling polymers and active pharmaceutical ingredients.

48. The process of claim 47, further comprising applying one or both of a seal layer between the core and the coating layer, between the one or more coating layers, and over the coating layers.

49. The process of claim 47, wherein the core comprises an inert core.

50. The process of claim 47, wherein the core and one or more coating layers comprise one or more pharmaceutically acceptable excipients.

51. The process of claim 47, wherein the core is prepared by extrusion-spheronization.

52. The process of claim 51, wherein the extrusion-spheronization process comprises granulating an inert core material with or without other pharmaceutical excipients with a binder solution to form a wet mass;

passing the wet mass through an extruder to form extrudates; and

spheronizing the extrudates.

53. The process of claim 47, wherein the core is prepared by granulation.

54. The process of claim 53, wherein the granulation process comprises wetting a dry mix of core material with or without other pharmaceutical excipients with a binder solution.

55. The process of claim 47, wherein the units are prepared by coating the cores with active pharmaceutical ingredients and rate controlling polymers.

56. The process of claim 47, wherein the units are prepared by coating cores with a first layer comprising an active pharmaceutical ingredient and a second outer layer comprising a rate controlling polymer.

57. The process of claim 47, further comprising applying a seal coat layer between the core and the subsequent layers or between a layer comprising an active pharmaceutical ingredient and a layer comprising a release rate controlling polymer.

58. The process of claim 57, wherein the release rate controlling polymer comprises one or more of sustained release polymers and one or more of enteric polymers.

59. The process of claim 58, wherein the sustained release polymer comprises one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethyl phthalate, cellulose acetate phthalate, and mixtures thereof.

60. The process of claim 59, wherein the sustained release polymer is a combination of ethyl cellulose and hydroxypropyl methylcellulose.

61. The process of claim 58, wherein the enteric polymer comprises one or more of cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl phthalate,

hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers, and mixtures thereof.

62. The process of claim 61, wherein the enteric polymer is a methacrylic acid copolymer.

63. The process of claim 47, wherein the active pharmaceutical ingredient comprises carvedilol.

64. The process of claim 47, wherein the dosage form comprises a tablet.

65. The process of claim 47, wherein the dosage form comprises a capsule.

66. A process for the preparation of controlled release multiple unit system of carvedilol comprising the steps of:

a. coating inert core with carvedilol and rate controlling polymer layer;

b. optionally applying a seal coat between inert core and carvedilol layer, and/or carvedilol layer and rate controlling polymer layer, and/or over the rate controlling polymer layer; and

c. processing into a solid dosage form.

67. The process for the preparation of controlled release multiple unit system of claim 66, wherein the rate controlling polymer layer is applied as a homogeneous coating composition.

68. The process for the preparation of controlled release multiple unit system of claim 67, wherein the rate controlling polymer layer is applied as solution.

69. The process for the preparation of controlled release multiple unit system according to claim 66, wherein the carvedilol layer and seal coat layers are applied as a solution/suspension.

70. The process for the preparation of controlled release multiple unit system of claim 68 or 69, wherein the solution or the suspension is prepared in a solvent.

71. The process of claim 70, wherein the solvent is selected from one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, and water.

72. The process for the preparation of controlled release multiple unit system of claim 66, wherein wherein the coating layers are applied using a hot melt technique.

73. The process for the preparation of controlled release multiple unit system of claim 66, wherein the solid dosage form comprises one or more of a tablet, a capsule, and a sachet.

74. The process for the preparation of controlled release multiple unit system of claim 32, wherein the solid dosage form is a capsule.

75. A method for treating congestive heart failure and/or hypertension in a subject, by administering to said subject, a controlled release multiple unit system of carvedilol comprising an inert core coated with a carvedilol layer; and a rate controlling polymer layer comprising one or more of sustained release polymers and one or more of enteric polymers.

76. A method for treating congestive heart failure and/or hypertension in a subject, by administering to said subject, a controlled release multiple unit system of carvedilol comprising an inert core coated with a carvedilol layer; and a rate controlling polymer layer comprising one or more of sustained release polymers and one or more of enteric polymers, wherein the rate controlling polymer layer is applied as a homogeneous coating composition.